(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 February 2002 (28.02.2002)

PCT

(10) International Publication Number
WO 02/16347 A1

(51) International Patent Classification[7]: C07D 401/12, A61K 31/505, A61P 25/24

(21) International Application Number: PCT/EP01/09498

(22) International Filing Date: 16 August 2001 (16.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00307224.6 22 August 2000 (22.08.2000) EP

(71) Applicant *(for all designated States except US)*: **AKZO NOBEL N.V.** [NL/NL]; Velperweg 76, NL-6824 BM Arnhem (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **RIDER, Peggy, Hester** [US/US]; 16, Willow Drive, Randolph, NJ NJ 07869 (US). **PLOEMEN, Joannes, Hubertus, Toussaint, Maria** [NL/NL]; Maasstaete 35, NL-6585 CB MOOK (NL). **HILL, David, Robert** [GB/GB]; c/o Organon Laboratories Ltd., New Edinburgh Road, Newhouse, Lanarkshire, Central Scotland ML1 5SH (GB). **SHAHID, Mohammed** [GB/GB]; c/o Organon Laboratories Ltd., New Edinburgh Road, Newhouse, Lanarkshire, Central Scotland ML1 5SH (GB). **WARD, Nicholas, Matthew** [GB/GB]; c/o Organon Laboratories Ltd., New Edinburgh Road, Newhouse, Lanarkshire, Central Scotland ML1 5SH (GB). **DRINKENBURG, Wilhelmus, Helena, Ignatius, Maria** [NL/NL]; Schoolstraat 1, NL-5124 RM Molenschot (NL).

(74) Agent: **KRAAK, Hajo**; Patent Department, P.O.B. 20, NL-5340 BH Oss (NL).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*
— *entirely in electronic form (except for this front page) and available upon request from the International Bureau*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/16347 A1

(54) Title: ACTIVE METABOLITE OF GEPIRONE

(57) Abstract: The invention relates to 3-OH-gepirone, or a pharmaceutically acceptable addition salt thereof, for use in therapy, to a pharmaceutical composition of 3-OH-gepirone and to the use of 3-OH-gepirone in the manufacture of a medicament having psychotropic activity, in particular for the treatment of depression or related disorders.

ACTIVE METABOLITE OF GEPIRONE

The invention relates to a compound for use in therapy and to a pharmaceutical composition having psychotropic activity.

Disorders of the central nervous system, such as depression and anxiety are illnesses that affect people of all ages. Although there are many effective drugs available for treatment of these diseases, the currently available methods of treatment are often still not adequate. Most noteworthy is that there are no positive treatment results in about one third of all subjects with depression or anxiety and recovery in the effectively treated group is slow, with an onset of effect at the earliest two weeks after the start of drug treatment. Also the side effects remain a cumbersome problem. The strategy for finding new drug therapies is to explore new pharmacological mechanisms of action. A compound with a new mechanism of action and efficacy for treatment offers better treatment possibilities for a large number of people. Gepirone (disclosed in US patent 4,423,049) is an example of a modern drug for the treatments of depression and anxiety with a newer mechanism based on an influence of a particular subtype of serotonin receptors. It remains however uncertain whether the action of the compound is due to an activation or an antagonism of the 5-HT_{1A} receptors, since the compound is a partial 5-HT_{1A} agonist. It might even be that the partial character of the agonism or antagonism is essential. For this reason it is all the more surprising that it is found that a metabolite of gepirone, 3-OH-gepirone (Kerns et al J. Pharmaceut & Biomedical Analysis, Vol 20, pp 115-128, 1999), is having a major central nervous system effect and is formed in significant quantities after administration of gepirone. The pharmacology of 3-OH-gepirone differs from the pharmacology of gepirone showing that with 3-OH-gepirone a more purposeful mechanistic treatment of psychiatric diseases can be obtained.

Therefore, this invention makes 3-OH-gepirone, or a pharmaceutically acceptable addition salt thereof, available for therapy.

3-OH-gepirone is a shorter name for the compound 3-Hydroxy-4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2,6-piperidinedione, which has a (+) and a (-) enantiomer. Consequently it exists as racemic

mixture or as one of the enantiomers in pure form or even as a mixture of the two enantiomers in various proportions of each of the enantiomers. Any of such forms are provided by this invention and referred to in this description by the term 3-OH-gepirone. Only in the section of the examples the information specifically refers to the racemic mixture.

It is a preferred embodiment of this invention to make a pharmaceutical composition of 3-OH-gepirone, or a pharmaceutically acceptable addition salt thereof, in association with one or more pharmaceutically acceptable carriers available.

Thus it is an aspect of the invention to use 3-OH-gepirone, or a pharmaceutically acceptable addition salt thereof, in the manufacture of a medicament having psychotropic activity, this medicament preferably being made acceptable for the treatment of depression or related disorders and it is a further aspect of the invention that it provides for a method for the treatment of depression or a related disorder in an individual of a vertebrate species which comprises treating said individual with an effective amount of 3-OH-gepirone, or a pharmaceutically acceptable addition salt thereof.

The following specifications of the terms used above serve to clarify better what is provided by this invention.

Unless otherwise stated all amounts of the active component refer to the weight of gepirone as base. According to the terminology in this description the drug gepirone, or a pharmaceutically acceptable addition salt thereof, is the active ingredient or active component in a pharmaceutical formulation.

Pharmaceutically acceptable addition salts include acid addition salts, for example, hydrochloric, fumaric, maleic, citric or succinic acid, these acids being mentioned only by way of illustration and without implied limitation.

The terms pharmaceutically acceptable carriers and excipients refer to

those substances known in the art to be allowable as filler or carrier material in pills, tablets, capsules etc. The substances are usually approved for this purpose by health-care authorities and are inactive as pharmacological agents. A compilation of pharmaceutically acceptable carriers and excipients can be found in the Handbook of Pharmaceutical excipients (2nd edition edited by A. Wade and P.J. Weller; Published by the American Pharmaceutical Association, Washington and The Pharmaceutical Press, London in 1994). Specifically, lactose, starch, cellulose derivatives and the like, or mixtures thereof, can be used as carriers for the active components of the combination according to this invention.

The effect of gepirone is usually referred to as an anti-depressant effect, implying mood improving effects in depressed patients. However the effect of this drug is not limited to an effect in depressed patients. Certain other diseases and symptoms influenced by the central nervous system are also known to improve with treatment with gepirone. In more general terms, this drug has psychotropic activity. The latter term refers here to any effect on the functioning of the central nervous system, useful to influence behaviour and feelings of well-being of mammals, in particular humans.

The term 'depression and related disorders' refers to a medical field which can be understood by the skilled person by his knowledge of the current use of anti-depressant drugs. Those disorders known to respond positively to treatment with drugs classified as antidepressants are considered for the description of this invention as being related to depression. Such disorders are for example anxiety disorders, such as panic disorder, obsessive compulsive disorder, posttraumatic stress disorder, or chronic pain syndromes. It is well known that anti-depressant drugs have more general beneficial effects on behaviour and mental functioning which is not strictly limited to an effect on depression. Also included in the invention is the use in anxiety in the manner in which anti-depressant drugs are used, that is with extended use for a long term effect, which is to be distinguished from the use of typical anxiolytic drugs, also referred to as minor tranquillisers, which have an

acute anxiety relieving and often sedative effect. The latter anxiolytic/sedative effect is usually ascribed to interactions with the GABA-receptor in the brain.

Such pharmacological information can lead to placement of drugs in different categories. Independent from the medical categories 'anxiolytic, 'anti-depressant', 'neuroleptic' etc., or the chemical categories 'tetracyclics', 'benzodiazepines' etc., drugs can be categorised on basis of pharmacological mechanism. In this sense gepirone is known as a 'partial 5-HT_{1A}-agonist'. This description should not be interpreted to imply any theory justifying the placement of the new pharmacological profile of 3-OH-gepirone in a particular new or known pharmacological category.

While it is possible for 3-OH-gepirone to be administered as the pure chemical, it is preferable to present it as a pharmaceutical composition, also referred to in this context as pharmaceutical formulation. Suitable compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. Pharmaceutical compositions according to the present invention comprise 3-OH-gepirone together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents.

As mentioned an important aspect of the present invention is that it provides a method for the treatment of an individual of a vertebrate species, for example, a mammal including a human patient, suffering from depression or a related disorder, which method of treatment comprises administering an effective amount of 3-OH-gepirone, or a pharmaceutically acceptable addition salt thereof. The desired daily doses for a treatment is preferably presented as a single dose or in two, or three sub-doses administered at appropriate intervals throughout the day. In practice this means among others to provide dosage units comprising 3-OH-gepirone for administration to a recipient or intake by a recipient for treatment.

Thus, in one embodiment of the invention 3-OH-gepirone may be

presented as a pharmaceutical formulation in unit dosage form, for example, administered in the form of a tablet, pill, capsule and the like. Such dosage forms and their methods of preparation are known in the art, e.g. as described in the standard reference, Gennaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture). By means of pharmaceutically suitable liquids the compound can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray.

For the preparation of pharmaceutical compositions and more specifically dosing units, the present invention further includes a process for the preparation of a pharmaceutical formulation comprising 3-OH-gepirone, which process comprises bringing an amount of 3-OH-gepirone (or a pharmaceutically acceptable salt thereof) into association with one or more pharmaceutical excipients.

For the use of the 3-OH-gepirone according to the present invention the compound should be provided such that an effective amount for treatment is made available. The amount of 3-OH-gepirone (or a pharmaceutically acceptable salt or solvate thereof), required to produce the efficacious effects will, of course, vary and is ultimately at the discretion of the medical practitioner. The factors to be considered include the route of administration and nature of the formulation, the recipient's body weight, age and general condition and the nature and severity of the disease to be treated.

In general, a suitable dose of 3-OH-gepirone for administration to a human will usually be in the range of from 0.01 to 3 mg per kilogram body weight of the recipient per day, preferably in the range of from 0.05 to 0.7 mg per kilogram body weight per day.

Formulations suitable for oral administration may be presented as discrete units such as pills, tablets or capsules each containing a predetermined amount of active ingredient(s); as a powder or granules; as a solution or suspension. The active ingredient(s) may also be present as

a bolus or paste, or may be contained within liposomes.

Formulations for rectal administration may be presented as a suppository or enema.

For parenteral administration, suitable formulations include aqueous and non-aqueous sterile injection. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed vials and ampoules, and may be stored in a freeze dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example, water prior to use.

Formulations suitable for administration by nasal inhalation include fine dusts or mists which may be generated by means of metered dose pressurised aerosols, nebulisers or insufflators.

For making dosage units, e.g. tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. Suitable amounts of active ingredients are, for example, a tablet comprising 1 to 30 mg of 3-OH-gepirone. In a specific example, a tablet comprising 10 mg of 3-OH-gepirone is obtained.

3-OH-gepirone may be prepared according to the method described in example 1.

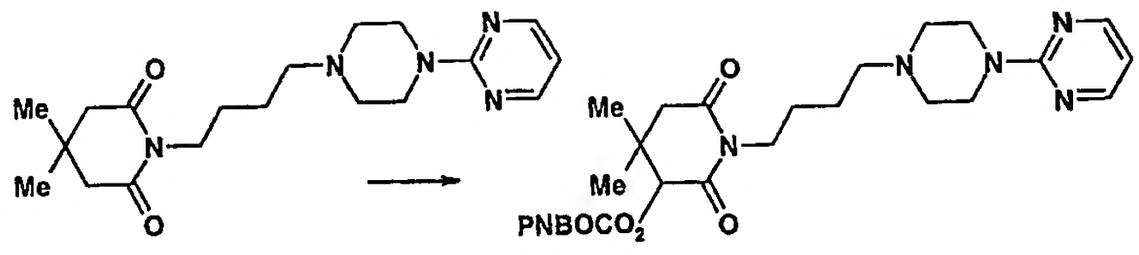
The invention is further illustrated by the following examples.

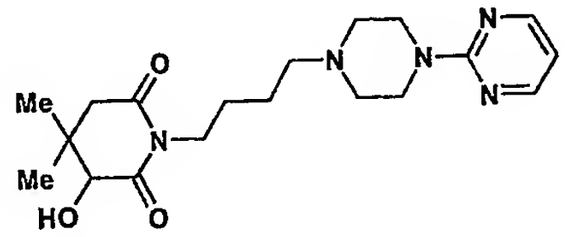
Example 1

Synthesis of 3-OH-gepirone

The synthesis of (+/-)-3-Hydroxy-4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2,6-piperidinedione, 3-Hydroxy-Gepirone.

Reaction Scheme:





Lithium bis(trimethylsilyl)amide (1M solution in THF, 38.2ml) was added over 10 minutes to a stirred solution of 4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperiazinyl]butyl]-2,6-piperidinedione ("Gepirone free-base") (12.7g) in tetrahydrofuran (200ml) at –40°C under nitrogen. After a further 2hours 30 minutes, a solution of bis(4-nitrobenzyl)peroxydicarbonate (*J.A.C.S.*, 1950, 72, 1254).(15g) in tetrahydrofuran (100ml) was added dropwise over 10 minutes. After 1 hour the temperature was allowed to rise to –20°C and water (100ml) was added dropwise. The mixture was allowed to warm to room temperature and then extracted with ethyl acetate (500ml). The organic extract was dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed through a column of fine silica in ethyl acetone : acetone mixtures. The appropriate fractions were combined and evaporated to dryness to afford 4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2,6-piperidinedione-3 (4-nitrobenzyl)-carbonate as a gum (6.6g).

A solution of 4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2,6-piperidinedione-3 (4-nitrobenzyl)-carbonate (8.1g)) in tetrahydrofuran (85ml) and methanol (85ml) was stirred for 50 minutes under an atmosphere of hydrogen (2 Barr) in the presence of 5% palladium on charcoal. The reaction mixture was filtered and the filtrate was evaporated to dryness in a water bath at <10°C. The residual oil was chromatographed through a column of fine silica in ethyl acetate :

acetone mixtures. The appropriate fractions were evaporated to dryness and the residue (4.4g) was crystallised from acetone : heptane to afford (+/-)-3-Hydroxy-4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2,6-piperidinedione, ("3-Hydroxy-Gepirone"), as a white solid (3.8g), m.p. 128°C.

Example 2

Binding Serotonergic Receptors

The data from the experiments using cloned human 5HT receptors is shown in Table 1. It is clear that 3OH-gepirone shows high selectivity for binding to $5HT_{1A}$ receptors when compared to $5HT_{2A}$, $5HT_{2C}$ and $5HT_6$ receptors.

Table 1. Gepirone and 3OH-gepirone binding activity at serotonin receptors

	Test Compounds					
	Gepirone			3OH-Gepirone		
	PKi	n	sem	pKi	n	sem
$5HT_{1A}$	7.42	5	0.03	7.24	3	0.06
$5HT_{2A}$	<5.20	5	-	5.70	3	0.05
$5HT_{2C}$	<5.03	5	-	<4.05	3	-
$5HT_6$	<4.30	4	-	<4.26	3	-
$5HT_7$	6.20	4	0.07	5.75	3	0.02

sem: Standard error of the mean

n: number of observations

Example 3

DRL72: Test for Antidepressant-like Activity

Gepirone and 3-OH-gepirone altered performance in the DRL72 in a manner consistent with an antidepressant-like profile (see Table 2). Gepirone and 3-OH-gepirone increased the number of reinforcements earned during the test session and decreased the number of responses at 3 mg/kg.

Table 2 Gepirone and 3-OH-gepirone exhibited antidepressant-like properties in DRL72. Key ↑ increased relative to control, ↓ decreased relative to control, ↔ unchanged relative to control.

Compound (doses mg/kg)	Indication	Number of reinforcements (MED mg/kg)	Number of responses (MED mg/kg)
gepirone (1, 3, 10)	Antidepressant	↑ (3)	↓ (3)
3OH-gepirone (1, 3, 10)	Antidepressant	↑ (3)	↓ (3)

MED: Minimum effective dose

Example 4

Automated Classification of Sleep Organization (ACSO): Test for CNS and Therapeutic Activity

EEG test

The aim of this test was to characterise the effects on rat sleep-waking behaviour of gepirone and 3-OH-gepirone. Sleep-waking behaviour was analysed by using electroencephalographic (EEG) recordings, electromyographic (EMG) recordings, and by recording a movement index. On the basis of these signals sleep-waking behaviour was automatically classified per 2 second periods into 6 classes: active waking, passive waking, light sleep, deep sleep, intermediate stage sleep and REM sleep (Ruigt et al. A large scale automated system for rat sleep staging. I. Methodology and technical aspects. Electroenceph. and Clin. Neurophysiol.; 1989; 73:52-64).

Each experiment is performed simultaneously on 32 adult male Sprague-Dawley rats (Harlan Olac, Bicester, UK, weighing 250-800 g), subdivided into four treatment groups. Throughout the whole experiment the animals stay in recording cages and are only taken out to be injected

with vehicle or test compound(s). Each experiment contains three sessions. The first session ("test session"), commencing at 10:00 AM with a variable duration of 2-5 hours, serves as adaptation period and is used to assess the quality of the EEG and EMG signals recorded. The second and third sessions both start at 2:30 PM on two consecutive days and have a duration of 15.5 hours each. At the start of the second session all groups receive a vehicle treatment, at the start of the third session all groups receive their test compound(s). One of the treatment groups usually receives the vehicle treatment in both sessions to serve as a baseline for the other groups in the experiment. The gepirone was dissolved in 0.9% NaCl m/v in water (saline). 3OH-gepirone was administered in 5% Mulgofen in saline (0.9 % NaCl)

Independently, in a comparable way a large number of reference compounds (Ruigt et al., Computer-based prediction of psychotropic drug classes based on a discriminant analysis of drug effects on rat sleep. Neuropsychobiology; 1993; 28:138-154) from different psychotropic drug classes (antidepressant [AD], antipsychotic [APS], hypnotic [HYP], anxiolytic [AXL], stimulant [STIM], anticonvulsant [AC]) was previously tested at different doses against placebo [PLAC] for their effects on rat sleep-waking behaviour. The effect profiles for these compounds at active doses were subjected to a discriminant analysis over these 6 psychoactive classes with placebo being added as an extra class.
Gepirone tested at 1.0, 3.0, 10.0 mg/kg i.p. induced dose dependent changes in the pattern of sleep-wake state distribution that had a quick onset and were indicative of anxiolytic and antidepressant-like properties (see table 3). Most pronounced were the reduction in REM sleep, the increase in passive waking, and the prolongation of REM sleep latency. Gepirone also increased waking and decreased sleeping, a pattern that suggests a non-sedative profile with mild stimulant properties.

To further characterise the central activity of 3-OH-gepirone this compound was investigated on rat sleep-waking behaviour at comparable doses (1.0, 3.0, and 10.0 mg/kg i.p.). 3-OH-gepirone showed a characteristic profile of activity at 10 mg/kg. 3-OH-gepirone reduced REM sleep, increased REM latency and passive waking at 10 mg/kg. A

discriminant function indicated that 10 mg/kg of 3-OH-gepirone closely resembles an antidepressant-profile with anxiolytic properties.

Table 3 The effects of gepirone and 3-OH-gepirone on sleep-wake organisation (0-3 hours after drug administration) and drug classification according to a discriminant analysis based on established reference compounds.

	Dose (mg/kg)	Drug classification	REM	REM latency	PW	AW	DS	LS	IS
Placebo	0	PLAC: 34	-	-	-	-	-	-	-
Gepirone	1	PLAC: 35	-	-	-	↓	-	-	-
	3	AD: 28	↓	↑	↑	-	-	-	-
	10	AXL: 63	↓	↑	-	-	↓	-	↓
Placebo	0	PLAC: 31	-	-	-	-	-	-	-
3-OH-gepirone	1	PLAC: 41	-	-	-	-	-	↑	-
	3	AC: 53	-	-	↑	-	-	-	-
	10	AD: 55	↓	↑	↑	-	-	↓	↓

Key (7 drug classification categories): AD = antidepressant; APS = antipsychotic; STIM = stimulant; AXL = anxiolytic; HYP = hypnotic; AC = anticonvulsant; PLAC = placebo; REM = rapid eye movement; PW = passive waking; AW = active waking; DS = deep sleep; LS = light sleep, IS = intermediate sleep. ↑ Increased or ↓ decreased relative to control.

Example 5

Marble Burying and Swim-Induced Grooming: Tests for Antidepressant/ Anxiolytic-Like Activity

Marble burying has been developed and validated as a pre-clinical assay of potential anxiolytic activity (Andrews and Broekkamp (1993). Procedures to identify anxiolytic or anxiogenic agents. In *Behavioural Neuroscience*, ed. A Sahgal, pp. 37-54. IRL Press, Oxford). The marble burying test places a naive mouse into a novel environment containing 25 marbles (arranged on top of a saw dust surface). A reduction in the

number of marbles buried by the mouse has been hypothesised to be an anxiolytic-like/anti-depressant-like effect.

Grooming behaviour of mice after swimming in lukewarm water is a reproducible behaviour. Compounds with antipsychotic activity can suppress this grooming and are more effective in reducing this behaviour than in reducing burying behaviour provoked by glass marbles. The aim of this test is to evaluate the ability of 3OH-gepirone to inhibit this behaviour. Male MF1 (24-32 g, Harlan Olac, Bicester, UK) were used. The experiment was performed in a draught-free room with 4 groups of 8 animals, each of which received different doses of the test drug or vehicle control subcutaneously. After 30 minutes they are placed in groups of four in swimming cages consisting of macrolon cages (type 2; 23cm x 17cm x14cm), each filled with 10cm of water at 37°C. Following this period the mice are removed from the water, dried with a towel and placed individually in 8 observation cages (Macrolon type 2 cages; 23cm x 17cm x14cm). Grooming behaviour is scored using a time sampling method, every 30 seconds over 15 minutes, and the sum of the positive observations yields the grooming score.

The experiment is carried out as a randomised block design with 4 blocks of 8 mice each (4 treatment groups with 8 mice each). For each treatment group the median grooming score is calculated together with 25% interquartile ranges. The Mann-Whitney U-test is used on the grooming score to calculate significance between the control and compound groups. When there are differences between blocks, a Mann-Whitney U-test for block design is applied. The median grooming score of each compound group is also expressed as percentage inhibition of the median grooming score of the control group. The ED_{50} (effective dose causing 50% inhibition of grooming) is derived using a 4-parameter logistic fit. 3OH-gepirone was administered in 5% Mulgofen in saline (0.9 % NaCl). Route of administration: subcutaneously (s.c.), 10ml.kg^{-1}. (30 minutes s.c. pretreatment)

Gepirone and 3-OH-gepirone reduced marble burying in mice following subcutaneous administration. The marble burying test is sensitive to drugs with sedative, antipsychotic, anxiolytic and antidepressant properties. Furthermore, 3-OH-gepirone reduced marble burying with greater potency than that observed for inhibition of swim induced

grooming (see Table 4).

Table 4: gepirone and 3OH-gepirone reduced marble burying behaviour in mice, the results suggest anxiolytic/antidepressant-like activity

Compound	Reduction in marble burying (ED_{50} mg/kg)	Inhibition of swim induced grooming (ED_{50} mg/kg)
gepirone	2.16	n.t.
3OH-gepirone	2.59	4.15

n.t.: Not tested

Claims

1. 3-OH-gepirone, or a pharmaceutically acceptable addition salt thereof, for use in therapy
2. A pharmaceutical composition of 3-OH-gepirone, or a pharmaceutically acceptable addition salt thereof, in association with one or more pharmaceutically acceptable carriers.
3. Use of 3-OH-gepirone, or a pharmaceutically acceptable addition salt thereof, in the manufacture of a medicament having psychotropic activity.
4. The use according to claim 3, characterised in that the medicament is for the treatment of depression or related disorders.
5. A method for the treatment of depression or a related disorder in an individual of a vertebrate species which comprises treating said individual with an effective amount of 3-OH-gepirone, or a pharmaceutically acceptable addition salt thereof.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 01/09498

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 A61K31/505 A61P25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 423 049 A (TEMPLE JR DAVIS L) 27 December 1983 (1983-12-27) cited in the application example 7	1-5
Y	US 4 956 368 A (CIPOLLINA JOSEPH A ET AL) 11 September 1990 (1990-09-11) table 3	1-5
Y	CIPOLLINA ET AL.: "Synthesis and biological activity of..." J.MED.CHEM., vol. 34, 1991, pages 3316-3328, XP002157852 see compound 42, table 1 and page 3323	1-5

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 January 2002	07/02/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 01/09498

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	KERNS ET AL.: "Monitoring in vitro experiments using..." J.PHARM.BIOMED.ANAL., vol. 20, 1999, pages 115-128, XP000972965 cited in the application page 117	1-5
P,X	WO 01 45687 A (FABRE LOUIS F ;FABRE KRAMER PHARMACEUTICALS I (US); KRAMER STEPHEN) 28 June 2001 (2001-06-28) claim 1	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern: al Application No
PCT/EP 01/09498

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4423049 A	27-12-1983	AT 382373 B	25-02-1987
		AT 469882 A	15-07-1986
		AU 555797 B2	09-10-1986
		AU 9108382 A	07-07-1983
		BE 895504 A1	28-06-1983
		CA 1244426 A1	08-11-1988
		CH 656383 A5	30-06-1986
		CY 1379 A	07-08-1987
		DE 3248160 A1	07-07-1983
		DK 573182 A ,B,	29-06-1983
		ES 518510 D0	16-06-1984
		ES 8405786 A1	01-10-1984
		ES 524945 D0	01-08-1985
		ES 8506696 A1	16-11-1985
		FI 824442 A ,B,	29-06-1983
		FR 2518993 A1	01-07-1983
		GB 2114122 A ,B	17-08-1983
		GR 77045 A1	04-09-1984
		HK 5288 A	29-01-1988
		IE 54619 B1	20-12-1989
		IT 1158039 B	18-02-1987
		JP 6293753 A	21-10-1994
		JP 1703754 C	14-10-1992
		JP 3068875 B	30-10-1991
		JP 58118582 A	14-07-1983
		KE 3709 A	16-04-1987
		KR 8701045 B1	26-05-1987
		LU 84561 A1	08-09-1983
		NL 8204970 A ,B,	18-07-1983
		PT 76036 A ,B	01-01-1983
		SE 453088 B	11-01-1988
		SE 8207425 A	12-08-1983
		SG 29787 G	17-07-1987
		ZA 8208549 A	28-09-1983
US 4956368 A	11-09-1990	NONE	
WO 0145687 A	28-06-2001	AU 2268701 A	03-07-2001
		WO 0145687 A2	28-06-2001